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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,538	09/29/2003	Shimin Liu	N12-001	1846

7590 03/29/2005

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Bridgeport, CT 06605

EXAMINER	
WALLENHORST, MAUREEN	
ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/673,538	LIU ET AL.	
	Examiner	Art Unit	
	Maureen M. Wallenhorst	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

2. The abstract of the disclosure is objected to because it is not in single paragraph form. Correction is required. See MPEP § 608.01(b).

3. Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the recitation of a "strong reducing agent" is indefinite since there is no comparative basis for what constitutes "strong". See this same problem in claims 9, 12, 14, 26, 29, 31, 32, 33 and 34. In addition, in claim 1, the recitation of a "porphyrin-like product" is indefinite since it is not clear how this product differs from porphyrin itself. See this same problem in claims 9, 12, 14, 26, 29, 31, 32, 33 and 34.

Claims 3-4 are indefinite since it is not clear whether the recited percentages are percents by weight or percents by volume. See this same problem in claims 16-17.

On line 3 of claim 6, the word "or" should be changed to –and—so as to use proper Markush language. This same change should also be made in claims 10 and 19.

On line 3 of claim 13, the phrase "the fluorescence properties" lacks antecedent basis.

Claim 14 is indefinite since the recitations on lines 2-5 of the claim do not further limit the physical components of the kit, but merely recite functional method steps to be performed with the kit. The only positively recited physical component of the kit is a reacting solution containing a strong reducing agent. See this same problem in claims 31 and 34.

Claims 19-21 are indefinite since these claims do not further limit the structural or physical components of the kit, but merely limit method steps to be performed using the kit.

Regarding claim 22, the phrase "such as" on line 2 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 32 is indefinite since the preamble of the claim recites a method of determining whether a subject is at risk of developing or suffers from cerebral vascular trauma. However, the last step of the method does not relate back to this purpose of the method, but rather only recites that the fluorescence indicates the extent and spatial distribution of erythrocytes trapped in cerebral tissue microvasculature.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 6-8, 12, 14, 20-228, 31 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz (US Patent no. 4,378,971).

Schwartz teaches of a method and apparatus for quantitatively determining the level of hemoglobin in a biological sample. The method is used for diagnosing diseases in an individual such as intestinal tumors (see lines 24-26 in column 1 of Schwartz), and is used as an occult blood assay (see lines 57-59 in column 1 of Schwartz). The method comprises the steps of collecting a biological sample such as feces or urine, and combining the sample with a reacting solution specific for heme compounds such as hemoglobin. Schwartz teaches that if the sample is a feces sample, the sample should be homogenized in a saline solution. See lines 50-51 in column 8 of Schwartz. The reacting solution contains a strong reducing agent or salt. Schwartz teaches that the strong reducing agent is preferably ferrous oxalate or ferrous sulfate, but also indicates that other reducing agents may be used. See lines 37-48 in column 5 of Schwartz. The reducing agent causes the heme portion of hemoglobin to be converted to porphyrin. During the conversion reaction, iron is removed from the non-fluorescing heme-containing porphyrin, resulting in the iron-free fluorescing protoporphyrin, which fluoresces red upon exposure to ultraviolet light at a wavelenth of approximately 408 nm. Therefore, the removal of the iron from the porphyrin molecule in heme forms a porphyrin-like fluorescing compound, i.e. protoporphyrin. See lines 25-58 in column 6 of Schwartz. The fluorescence of the sample is

then measured with a fluorimeter or spectrofluorophotometer, and the fluorescing porphyrins are found to show fluorescence peaks between 500-630 nm. See lines 41-43 in column 7 and lines 3-21 in column 8 of Schwartz. Schwartz teaches that the fluorescence not related to the heme compound reaction in a biological sample must be removed from the sample in order to obtain an accurate measurement of the amount of hemoglobin or blood in a sample. See lines 55-68 in column 2 and lines 1-8 in column 3 of Schwartz. The measured fluorescence is compared with standard known levels of hemoglobin or protoporphyrin concentrations, and the concentration of the heme compounds or hemoglobin in the biological sample is calculated. Schwartz also teaches of a kit to be used in performing the method. The kit comprises a structure 18 having a plurality of reaction chambers 19a, 19b, 20a and 20b therein. These reaction chambers are provided with a cap 21 and a transparent window 22 that enables fluorescence of the material in the chambers to be assayed. Some of the chambers contain a reaction solution comprising a reducing agent. Biological test samples are then added to each of the chambers, where any heme compounds in the samples are reduced to a fluorescent protoporphyrin compound. Other of the chambers contain a non-reducing solution to serve as blank chambers that measure only naturally occurring fluorescence in a test sample. It is inherent in the kits taught by Schwartz that they contain instructions and protocols to be used with the components of the kit in order to perform a certain method, i.e. a method of determining blood products in a biological sample. See lines 61-68 in column 9 and lines 1-63 in column 10 of Schwartz.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 5, 9-11, 13 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz (US Patent no. 4,378,971). For a teaching of Schwartz, see previous paragraphs in this Office action. Schwartz fails to teach that the reacting solution contains saline therein, fails to teach that the method can be used to detect erythrocytes in a sample, and fails to teach of purifying a fecal sample before reacting the sample with the reducing agent.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to include saline in the solution of reducing agents taught by Schwartz since saline is disclosed by Schwartz as being used for homogenizing a fecal sample, and the inclusion of saline in the solution of reducing agents would avoid having to separately homogenize a fecal sample, and would allow a single solution to facilitate both the homogenization of a fecal sample and the reduction of the porphyrin molecules therein. It also would have been obvious to one of ordinary skill in the art to realize that the method taught by Schwartz can be used to detect erythrocytes in a biological sample since Schwartz teaches that the method is used to determine hemoglobin and heme compounds in a sample, and erythrocytes are well known as containing hemoglobin therein. Therefore, when hemoglobin is detected using the fluorescence method taught by

Schwartz, erythrocytes in the sample are also inherently detected since hemoglobin originates from erythrocytes. It also would have been obvious to one of ordinary skill in the art to purify fecal samples collected in the method taught by Schwartz in order to remove materials that might interfere with the production of an accurate fluorescence measurement since Schwartz teaches that fecal samples contain substances therein that produce fluorescence that is not related to the heme compound. By purifying the fecal samples, these compounds would be removed to obtain a value for fluorescence that is due specifically only to the porphyrin-like compounds formed from heme.

10. Claims 2-4 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz in view of Kerwin et al. For a teaching of Schwartz, see previous paragraphs in this Office action. Schwartz fails to teach that the reducing agent in the reacting solution can be sodium borohydride.

Kerwin et al teach of a storage stable hemoglobin solution. The solution contains therein, in combination with hemoglobin, a reducing agent. The reducing agent can be sodium borohydride. See lines 18-26 in column 5 of Kerwin et al. Kerwin et al teach that not all reducing agents can reduce hemoglobin (see lines 44-45 in column 2 of Kerwin et al), but that sodium borohydride is able to reduce hemoglobin by virtue of its inclusion in the composition.

Based upon the combination of Schwartz and Kerwin et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use sodium borohydride as the reducing agent in the method taught by Schwartz in place of ferrous oxalate or ferrous sulfate since Schwartz teaches that other known reducing agents that serve to reduce hemoglobin can be

utilized in the method, and Kerwin et al teach that sodium borohydride is a reducing agent that serves to reduce hemoglobin molecules.

11. Claims 29 and 32 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action since none of the prior art of record teaches or fairly suggests a method for determining the extent and spatial distribution of erythrocytes trapped in cerebral tissue microvasculature by treating a sample of cerebral tissue microvasculature with a strong reducing agent that reduces porphyrin to a porphyrin-like product, and monitoring for fluorescence in the treated tissue caused by the porphyrin-like product, wherein the measured fluorescence indicates the extent and spatial distribution of erythrocytes trapped in cerebral tissue microvasculature.

12. Claim 30 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims for the same reasons as given above.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Please make note of: Liu et al who teach of a method for visualizing trapped erythrocytes in a rat brain by treating brain tissue with sodium borohydride reducing agent, and monitoring fluorescence caused by porphyrin species located in erythrocytes. The article to Liu et al was published after the effective filing date of the instant application, and therefore, is not available as prior art against the instant claims.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 571-272-1266. The examiner can normally be reached on Monday-Wednesday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

March 23, 2005

Maureen M. Wallenhorst
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GROUP [redacted] 1700